Analytical Study of a Case Series of Vancomycin Associated Adverse Drug Reactions in Paediatric Population at a Tertiary Care Hospital: A Brief Report

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Abstract

Background: Red man syndrome (RMS) is frequently reported from pediatric ward in patients receiving vancomycin, at the medical store of SGH, Pune. Though common in pediatric patients, not all patients receiving vancomycin developed Red man syndrome. Hence, this study was done to analyse the demographic, pathophysiological, and pharmacological aspects of the subject who experience adverse drug reactions with vancomycin and to determine if this predisposition is associated with any of these factors.

Methods: All adverse drug reactions (ADR) to injection vancomycin in the pediatric ward that were reported from April 2018 - January 2022 were included. Controls were a similar number of randomly selected pediatric cases from the same ward who had received Intravenous vancomycin during the same period but did not experience the adverse drug reactions

Results: The mean age was 29.91 ± 34.87 months in subjects who experienced ADR and 57.37 ± 41.58 months, in non-ADR group (p=0.0286). 37.4% were infants, 29.69% toddlers in ADR Group. Seventy four percent of patients who manifested with ADR were below age of 3 compared to barely 38% in controls (p=0.03). 66.6% were malnourished in the ADR group compared to 27.6% in controls (p=0.007). There was no association between the ADR and ethnicity, religion, gender, diagnosis, co-morbidities, co-administered drugs, or administered dose of vancomycin among the children. There was no apparent seasonal variation in occurrence of the ADR.

Conclusion: TRMS is more common in paediatric population than adults and is usually uneventful. Around 75% of the reactions occur within first 4 days of start of Vancomycin and usually occurs within 30 min of the preceding dose. Younger age groups (infants) and malnourishment were the two factors significantly associated with occurrence of RMS. We may also consider using lower than conventional doses and much slower infusions in such at-risk population.

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Keywords: Adverse Drug Reaction; Vancomycin; Red Man Syndrome; Paediatric

Introduction

Vancomycin, a widely used bactericidal antibiotic, is obtained from Streptococcus orientalis (1). It acts by inhibiting cell wall synthesis and is exclusively active against aerobic Gram-positive organisms such as streptococci and staphylococci including MRSA and certain anaerobic bacteria (2). Parenteral vancomycin is primarily used for infections caused by methicillin-resistant Staph aureus (MRSA) or for Staph. epidermidis infections associated with the use of intravascular catheters. It is also effective for the treatment of Staph. enterocolitis and endocarditis. Red man syndrome is an infusion-related reaction peculiar to vancomycin (3, 4). It typically consists of pruritus, an erythematous rash that involves the face, neck, and upper torso. Less frequently, hypotension and angioedema can occur. Patients commonly complain of diffuse burning and itching and generalized discomfort. Signs of red man syndrome would appear about 4-10 min after an infusion started or may begin soon after its completion (5). It is often associated with rapid (<1 hour) infusion of the first dose of vancomycin (6). Delayed reactions at or near the end of a 90- or 120-min infusion have been seen in patients who had been on vancomycin therapy for longer than 7 days without prior incident (7). Literature states that the incidence varies between 3.7 and 47% in

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infected patients (3, 8). Studies of vancomycin also show that the most severe reactions occur in patients younger than the age of 40, particularly in children (9, 10). In Sassoon General Hospital, Pune complaints of rash and red discoloration of skin were often received following vancomycin administration as adverse events from paediatric ward. Despite the use of vancomycin in varied patient population, the ADR were mostly reported from paediatric department. Yet, though Red man syndrome was most frequently reported from the paediatric ward, it was not observed in all paediatric patients. Therefore, this retrospective study was designed to analyse association of ADR with the various demographic, pathophysiological and pharmacological factors.

Methods

This retrospective observational study of ADRs reported between April 2018 and January 2022 commenced after approval by the Institutional Ethics Committee of BJGMC & SGH, Pune (Ref No. BJGMC/IEC/Pharmac/ND-Dept 0321150-150 dt 26-03-2021). The investigation included all paediatric patients who reported experiencing ADR in the form of redness, a maculopapular rash, swelling, and pruritis after receiving intravenous vancomycin to the Main Medical Store, SGH, Pune between April 2018 and January 2022. A comparable number of randomly chosen paediatric cases from the same ward and time period who had received intravenous vancomycin but did not experience the ADR served as controls.

Case papers of the patients who satisfied the study criteria were obtained from the medical record section of Sassoon General Hospital, Pune. From their case reports, the essential information related to the demographic, clinical, pathological, and pharmacological data including per kg dose and infusion rate, was extracted, and entered into an excel spreadsheet. Prior to analysis, all records were delinked from the patient identifiers.

Patients who developed ADR were compared with patients who didn't develop ADR with respect to their demographic, clinical, pathological and pharmacological profile. Quantitative data was analysed using unpaired't' test in Microsoft Excel and qualitative data was analysed using the online Chi-Square test. $p< 0.05$ was considered significant.

Results

From April 2018 to January 2022, 32 adverse events following Injection vancomycin were reported to the Main Medical Store and Pharmacovigilance department of SGH, Pune. Five of the 32 ADRs were from adult patients and were therefore omitted since they did not fit the criteria for inclusion. Thus, 29 controls who received Injection vancomycin over the same period but did not develop ADR and 27 paediatric patients who experienced ADR after Injection vancomycin were included in the current investigation.

Table 1. Various parameters compared between ADR and Non-ADR group.

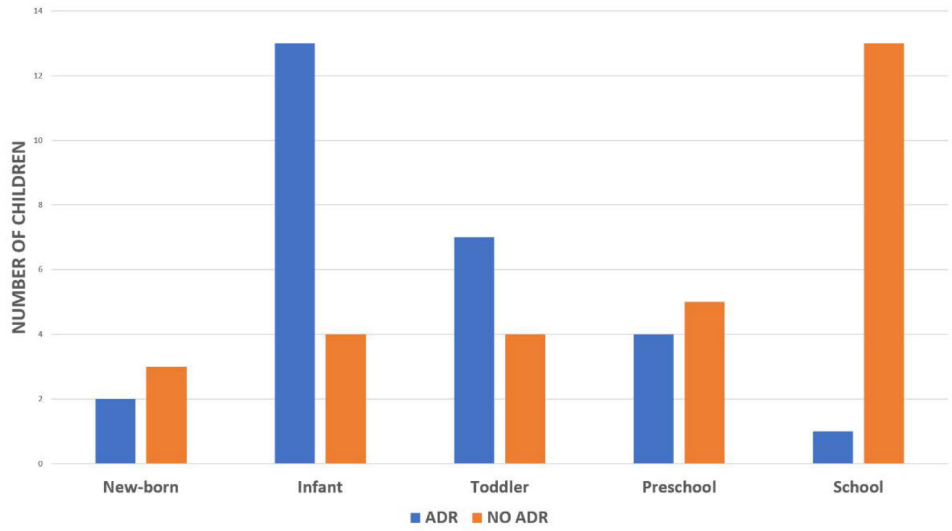
		ADR	NON-ADR	P VALUE
N		27	29	
SEX (Male: Female)		16:11	16:13	0.75747
AGE(MONTHS) Mean+SD		29.91 ± (34.87)	57.37 ± (41.58)	0.0286
Age	New-born	2	3	0.031606
	Infant	11	4	
	Toddler	7	4	
	Preschool	4	5	
	School	3	13	
Weight (kgs) Mean+SD		9.79 ± (7.56)	13.89± (7.470)	0.110
Religion	Hindu	19	24	
	Muslim	6	1	
	Christian	1	0	
	Buddhist	1	4	
Diagnosis	Respiratory	13	9	0.292
	CNS	7	13	
	Others	7	7	
Co- existing illness	Malnourished	18	8	0.007767
	Respiratory	3	1	
	CNS	4	2	
	CVS	3	1	
	Others	3	2	

Table 1. Continued

		ADR	NON-ADR	P VALUE
Dose per kg	20mg/kg	24	20	
	15mg/kg	3	6	
	10mg/kg	0	3	
Other Antibiotics given	Piperacillin-Tazobactam	10	9	0.702
	Meropenem	9	12	0.534
	Cefotaxime	5	10	0.1776
	Acyclovir	3	3	0.92619
	Anti-tubercular drugs HRZE	3	3	0.92619
	Chloroquine	1	3	0.595961
	Syrup Azithromycin	1	2	0.595

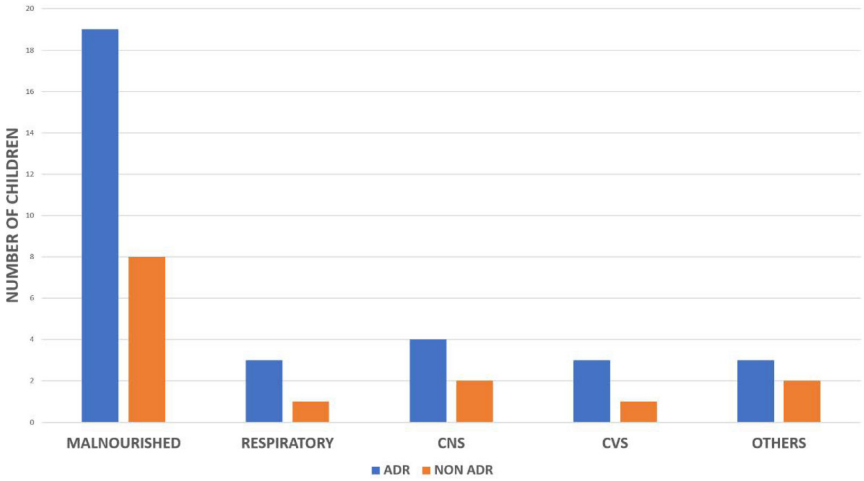
All subjects were of Indian origin. Amongst the patients who experienced the ADR following vancomycin infusion 70.3% patients were Hindu, 22% were Muslim, 3.7% were Christian /Buddhist while amongst the patients who did not experience the ADR following vancomycin infusion, 82.7% were Hindu, 3.4 % were Muslim and 13.7% were Buddhist. A chi square test of independence showed that there was no significant association between occurrence of ADR following Injection vancomycin and gender (p=0.757470) or religion. The mean weight for all subjects who experienced ADR in the study was 9.792± 7.56 and those who didn't experience ADR was 13.89±7.47 (p=0.110). The mean age was 29.91±34.87 months subjects who experienced ADR and 57.37±41.58 months, in those who didn't experience ADR p=0.0286 and suggesting that younger age was more likely to be associated with occurrence of the ADR Therefore, we further categorised the patients into various age sub-groups. Statistical analysis revealed that majority of patients who developed the ADR were infants (37.4%) followed by toddler (29.6.9%) and newborns (7.4%). Thus, around 74% of the patients who manifested with the ADR following Injection vancomycin were below the age of 3 years compared to barely 38% children who did not develop ADR following Injection vancomycin (p=0.034902).

Figure 1. Number of children across various age groups that experienced ADR & didn't experience ADR following injection vancomycin.



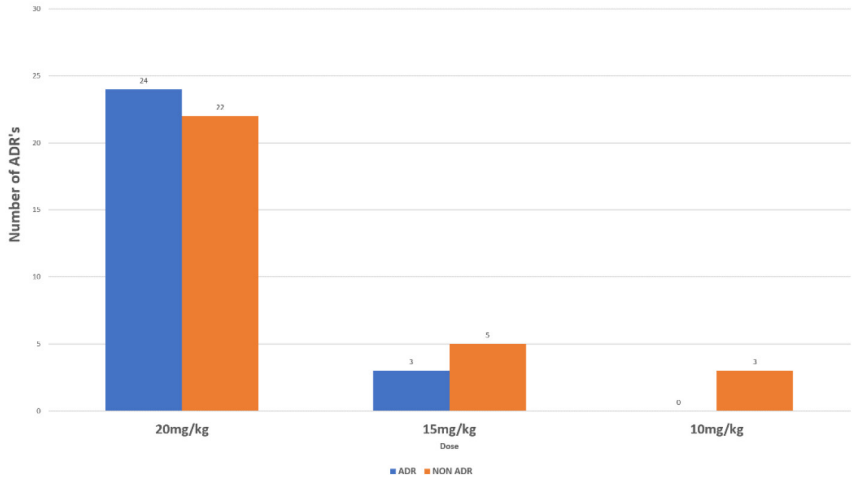
None of the study subjects had any previous history of allergy. There was a family history of relatives suffering from pulmonary tuberculosis in 14.8% of subjects who experienced ADR and 17.2% of subjects who didn't experience ADR (p=0.9068). In 48.14% of patients who experienced ADR, the diagnosis was Respiratory illness like bronchopneumonia, bronchiolitis, empyema and aspiration pneumonia, 25.9% it was neurological condition like meningitis and hydrocephalous with VP shunt and other disorders like B-cell Acute lymphoid leukemia, anaemia with failure to thrive and acute rheumatic fever in the rest 25.9% , while in the non-ADR group 31.03% were suffering from respiratory disorder, and 44.8% from neurological disorder (p=0.292) Two thirds of those who experienced ADR on vancomycin infusion were malnourished compared to 27.6% among those who did not develop ADR following Injection vancomycin (p=0.007791)

Figure 2. Number of children in both groups suffering from various co-existing illnesses.



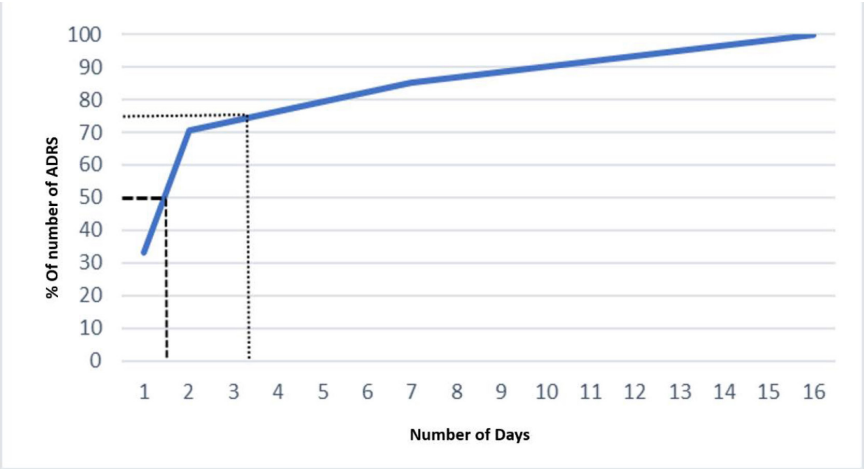
There was no significant relationship between the per kg dose of Vancomycin and occurrence of ADR.

Figure 3. Number of ADR'S vs. Dose per kg in ADR and Non ADR group.



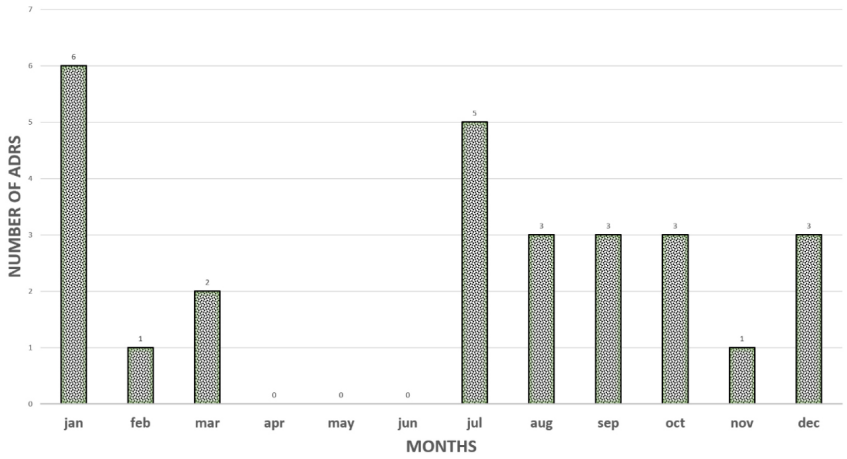
Similarly, there was no significant association between occurrence of the ADR and any of the co-administered drugs. Amongst those patients who developed ADR following Injection vancomycin, it was found that 50% of ADR's occurred within first 48 hrs and 75% of ADR's occurred within 4 days

Figure 4. % of number of adverse events vs number of days since start of vancomycin.



14 out of 27 (51.8%) developed reaction within first 30 minutes of receiving injection vancomycin. All patients showed remission of the ADR after discontinuation of vancomycin with or without supportive therapy 26 patients received treatment with Injection pheniramine and Hydrocortisone for the ADR while 1 did not require treatment following the ADR. Vancomycin was restarted in 11.11 % patients after remission of the ADR and was well tolerated. 27 ADRs occurred over a period of 3 years and when pooled together it was found maximum ADRs occurred in the month of January (22.2%) and July (18.5%) (Figure 5). This was done to check association with batch, However, no association was found with batch.

Figure 5. Distribution of ADR across various months.



Discussion

Sassoon General Hospital is a 1296 bedded tertiary care hospital which includes 50 beds in the paediatric ward. Vancomycin is routinely prescribed amongst adult and children in the hospital but it was observed that Red man syndrome was predominantly reported to pharmacovigilance cell from paediatric ward. During the period April 2018- January 2022, of the 32 ADRs that were reported following Injection vancomycin administration, 27 were from paediatric ward as compared to 5 from adult ward. Therefore, this retrospective study was designed to analyse association of ADR with demographic, pathophysiological and pharmacological factors, in an attempt to identify predictors/ predisposing factors for Red man syndrome in paediatric population. All subjects who experienced ADR reported pruritus, rash and flushing. Red man syndrome is the most frequent hypersensitivity reaction linked to vancomycin injection with incidence ranging from 3.7 to 47% (3, 8). Previous retrospective studies evaluated Red man syndrome in children who had been exposed to vancomycin and found a low rate (1.6%) of Red man syndrome, which limited their ability to determine risk factors (10). According to another study, a histamine-like rash appeared during the vancomycin infusion in seven or 35% of 20 individuals (11). Vancomycin-related adverse drug reactions (ADRs) studies have shown that individuals under the age of 40-particularly children-experience the most severe effects (10).

In our study, it was observed that in 50% of patients the reaction occurred within first 48 hours of initiating treatment with vancomycin; 75% of patients the reaction occurred within first 4 days of initiating treatment with vancomycin and remaining 25% had a delayed reaction. Among those who developed the reaction it was observed that 51.2% showed the reaction within 30 min of preceding dose of vancomycin. Also, remission of ADRs occurred after discontinuation of Vancomycin. Of the 27 patients who experienced ADR 26 received Injection Pheniramine and Injection Hydrocortisone while one showed remission without treatment. Previously available data show that African-American ethnicity was less likely to develop Red man syndrome as compared to Caucasians and other non-African American ethnic groups (10) but in our study since all patients were of Indian origin it was not possible to analyse the association of ethnicity with occurrence of ADR.

Though all patients were from paediatric population, when we analysed the association of the ADR with age, we found that the average age was smaller in people who developed ADR. So, we further sub classified the subjects as per paediatric age categories, and we found that majority of patients who developed the ADR following Injection vancomycin were below the age of 3 years. On the contrary, another study by Myers et al., on defining risk factors for red man syndrome in children and adults noted that children older than 2 years of age were 4.6 times more likely to develop Red man syndrome than children under 2 years of age and also that there was no difference found for development of Red man syndrome in those 2-16 years vs. >16-21 years of age (10). This difference could be due to wide variation in demographic characters and large sample size of their study. We found that the mean weight for all subjects who experienced ADR in our study was lower than those who didn't experience ADR and these findings were not statistically significant. Nevertheless, on analysis of co morbidities it was observed that two thirds of those who experienced

ADR on vancomycin infusion were malnourished compared to less than one third among those who did not develop ADR following Injection vancomycin (p= 0.008). Thus, suggesting that malnourishment could be one of the associated risk factors. Considering that in our study, the ADR was more prevalent in infantile age group which was contradictory to the study by Myers et al which said that Red man syndrome is more common in children above 2 years (10), we performed Mantel Haenszel analysis to assess whether malnutrition was confounding or modifying the results of age. The analysis revealed that malnutrition was an independent factor. A PubMed search revealed that no data was available on nutritional status being associated with vancomycin ADR in paediatric population. Thus, our study may be the first to analyse that nutritional status could be associated with Red man syndrome.

Another study has shown that subjects with underlying chronic co-morbid conditions were significantly more likely to develop Red man syndrome compared to healthy subjects (OR=1.8, 95% CI (1.1, 3.7), (p=0.032) (10) and no association was found with any specific chronic co morbid condition and development of Red man syndrome. However, in our study though co existing illness were common amongst those who developed ADR it did not achieve statistical significance and this could be due to small sample size of our study. Another Study has shown that patients with previous history of red man syndrome following exposure to vancomycin were more likely to develop Red man syndrome during current vancomycin therapeutic course (p<0.001) (10). However in our study, none of the patients had documented history of receiving vancomycin in the past. Therefore, we cannot comment on this aspect of risk for Red man syndrome. Studies have shown that vancomycin is much better tolerated when it is given in smaller and more frequent doses (14-17). Risk of red man syndrome is also associated with the concentration of vancomycin preparations with the 5 mg/ml preparation conferring lower risk of Red man syndrome than other preparations including 10 mg/ml, 50 mg/ml, 100 mg/ml (p<0.001) (10). However, in our study there was no statistically significant relationship between occurrence of ADR and dose of vancomycin. This could be due to small sample size in our study, but we definitely observed that in the group that experienced ADR all patients received vancomycin in doses more than15 mg/kg and none received 10mg/kg, while in those who didn't experience any ADR 10.3% received vancomycin in dose of 10mg/kg. Thus, our observations are consistent with these findings, however a larger sample size is required to confirm these findings. Literature mentions Red man syndrome is often associated with rapid (<1 hour) infusion of the first dose of vancomycin (15-17). In our study we cannot comment on rate being a contributing factor as all patient received the doses at 10mg/min over 30-60 minute. Also, in our study we found that 51.8% of the reactions occurred within 30 minutes of administration of Injection vancomycin. Other studies have found that Antibiotics such as ciprofloxacin, amphotericin B, rifampicin and teicoplanin (15) can potentially cause red man syndrome. In our study piperacillin, tazobactam, meropenem, cefotaxime, acyclovir, azithromycin rifampicin and ciprofloxacin were some of the co-administered drugs. However, on analysis of each drug separately we did not find any significant association between occurrence of the ADR and co-administration of drugs. This could again be due to small sample size of our study.

Hypotension was not observed in our patients unlike other studies where hypotension was also observed. (12-14). This difference could have been due to difference in race and age group of the patient's population.

Conclusions

Red man syndrome affects children more frequently than adults, yet it responds effectively to intravenous hydrocortisone and intravenous pheniramine. Most children show a reaction within 30 minutes of the previous vancomycin dose, and three-fourths of reactions happen within the first four days after starting vancomycin therapy. The two characteristics that were strongly linked with the occurrence of Red man syndrome in our study were younger age groups (infants) and malnourishment. Therefore, taking a little special caution during the first four days of starting vancomycin, particularly in younger children, such as infants and toddlers, and among the pediatric population who are malnourished, may help in the early detection of the Red man syndrome and help in preventing the complications of this adverse reaction. As a result of identifying age and nutritional status as potential risk factors for Red man syndrome, we can now consider utilizing lower than conventional doses and much slower infusions in the at-risk population, thus preserving the utility of an effective bactericidal antibiotic despite its known adverse effect.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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